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CORRESPONDENCE

Research Correspondence

Effect of Rosuvastatin on Fatigue in Patients With Heart Failure

To the Editor: It was recently reported that, compared with placebo, 6 months of treatment with a modest dose of simvastatin or pravastatin had an adverse effect on a summated measure of energy and fatigue in 1,016 generally healthy men and women (1). With a goal of verifying this observation, we conducted a retrospective analysis of the effect of a statin on fatigue in the 5,010 patients (1,180 women) with chronic systolic heart failure randomized to receive placebo or rosuvastatin 10 mg daily in the CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure) study. Fatigue was measured at baseline, 6 weeks, and 3 months thereafter in this older population.

The inclusion and exclusion criteria for CORONA have been described in detail elsewhere (2,3). Briefly, eligible patients were aged ≥60 years with symptomatic (New York Heart Association class II through IV), ischemic, systolic (left ventricular ejection fraction ≤40%) heart failure. The investigator was asked to rate patient fatigue "during the past few days" by using a 5-point scale (0 = none; 1 = on heavy exertion; 2 = on moderate exertion; 3 = on slight exertion; 4 = at rest). For the purposes of analysis, only change in fatigue from baseline to the 7.5-month follow-up visit was analyzed. This method was used to be most comparable to the study of Golomb et al. (1) and because after that time-point, significant numbers of patients experienced worsening heart failure or death. The difference between treatments for change in fatigue was compared by using a 2-sided Wilcoxon rank sum test, and proportions were compared by using chi-square tests. Statistical significance was set at a level of 0.05.

At baseline, the number of patients with grade 0, 1, 2, 3, and 4 fatigue was as follows: 233 (4.7%), 365 (7.3%), 1,940 (38.7%), 2,337 (46.7%), and 135 (2.7%), respectively. At 7.5 months, 4,653 (93%) patients had a measurement of fatigue compared with 5,010 patients at baseline. Figure 1 shows the proportions of patients reporting improvement, worsening, or no change in fatigue between baseline and 7.5 months of follow-up. Compared with placebo, 67 (2.8%) more statin-treated patients reported worsening of fatigue and 25 (1.2%) fewer reported improvement. Most showed no change (1,615 [69.1%] patients receiving rosuvastatin and 1,638 [70.7%] patients receiving placebo [overall p = 0.01]). Sex did not influence the effect of rosuvastatin (interaction tested in an ordinal logistic regression model p = 0.74). The number of patients reporting worsening of 2 or more categories was 50 (2.1%) in the rosuvastatin group and 52 (2.2%) in the placebo group (p = 0.81). The number of patients progressing to grade 3 fatigue over 7.5 months was 172 (7.4%) in the rosuvastatin group and 133 (5.7%) in the placebo group, a difference of 39 (1.7%) patients (p < 0.03). At 7.5 months, 946 (41%) rosuvastatin-treated patients and 919 (40%) patients receiving placebo had grade 3 fatigue (p = 0.56). The number of patients progressing to grade 4 fatigue over 7.5 months was 44 (1.9%) in the rosuvastatin group and 39 (1.7%) in the placebo group (p = 0.61); at 7.5 months, 70 (3.0%) rosuvastatin-treated patients and 66 (2.9%) patients receiving placebo had grade 4 fatigue (p = 0.76).

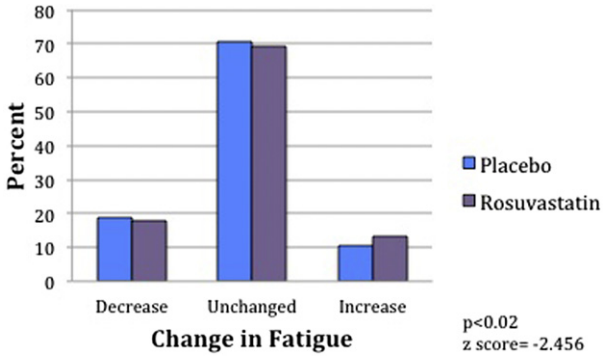

Figure 1 **Change in Fatigue Between Baseline and 7.5 Months of Follow-up**

Compared with placebo, a small excess (n = 67 [2.8%]) of statin-treated patients reported worsening of fatigue and 25 (–1.2%) fewer reported improvement; most showed no change (1,615 [69.1%] rosuvastatin-treated patients and 1,638 [70.7%] patients receiving placebo; overall p = 0.01).

In this post hoc analysis of a large, randomized, double-blind, placebo-controlled trial, we found some evidence that rosuvastatin leads to worsening fatigue although most patients assigned to statin treatment showed no change in fatigue (as was the case in the placebo group). There was no detectable excess of statin-treated patients reporting large changes (worsening of 2 or more categories) in fatigue, and only a small excess (43 more) showed progression to the most severe forms (grades 3 and 4) of fatigue. Consequently, the clinical significance of our findings is uncertain, especially because we studied elderly patients with systolic heart failure who might have been particularly vulnerable to the adverse effects of a statin. There were some other differences between our trial and that reported by Golomb et al. (1). We used a different statin, employed a simpler fatigue score (as opposed to a composite of "energy" and "fatigue with exertion"), and did not find an interaction with sex.

Although we believe our findings to be robust (we studied a large number of patients, had nearly complete observations, and did not have to impute missing data), the explanation of the findings is unclear; that is, it is uncertain why statins should cause fatigue. The most likely explanation is an effect on skeletal muscle;

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however, there is no convincing evidence that low-dose statins impair muscle function (4) or cause muscle-related adverse effectsmore frequently than placebo (as already reported in CORONA), except, perhaps, for very rare cases of rhabdomyolysis (5,6). Muscle-related adverse events are, however, clearly increased with high-dose simvastatin treatment (7). An alternative explanation is that statins might increase the perception of fatigue through a central nervous system effect, but this possibility is less likely with a hydrophilic agent such as rosuvastatin (8).

Although rosuvastatin led to worsening of fatigue in a small proportion of older patients with systolic heart failure, the clinical significance of this finding is uncertain.

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Letters to the Editor

Why Are We Still Using Coronary Bare-Metal Stents?

In their paper, Singla et al. (1) describe accurately the dilemma faced by cardiologists when confronted with a frequent occurrence in which a potential conflict may arise between the need for long-term dual antiplatelet therapy (DAPT) in recipients of drug-eluting stents (DES) and common real-life situations such as the need for noncardiac surgery.

Despite a wealth of data demonstrating the superiority of DES versus bare metal stents (BMS) in all types of lesions/patients (2), a significant proportion of patients still receive a BMS. One of the most frequent reasons is that implanting a BMS allows a 1-month duration of DAPT compared with a DES (6 to 12 months in the European Society of Cardiology guidelines, 12 months in the American Heart Association/American College of Cardiology guidelines) (3,4).

To elucidate why BMSs are still used today, we prospectively collected data from 31 centers in Europe and Asia to identify the main reason for implantation of BMS rather than DES in 744 consecutive percutaneous coronary interventions performed from April to May 2012. Eight indications for using BMS were identified: large vessel diameter, 241 (32.4%); ST-segment elevation myocardial infarction, 132 (17.7%); reimbursement/regulatory/other reasons, 70 (9,4%); advanced age, 92 (12.4%); concomitant oral anticoagulant treatment, 84 (11.3%); increased bleeding risk, cancer, or anemia, 71 (9.5%); planned noncardiac surgery within the next year, 41 (5.5%); and anticipated poor DAPT compliance, 13 (1.7%).

This demonstrated that the use of a BMS was directly driven by a concern about either bleeding or DAPT compliance in 301 (40.5%) cases. Although, as underlined by the authors, the risk of stent thrombosis is at its highest when DAPT discontinuation occurs during the first month after PCI, most interventions can be postponed for 1 month, and the selection between BMS and DES is then made in consideration of mid-term DAPT requirements (1 month only vs. 1 year).

This implies that a number of patients currently treated with a BMS can be considered to have been deprived of a more efficacious DES because of a concern about prolonged DAPT. Data have now become available to support a 3- to 6-month course of DAPT after DES implantation (5,6), but there is a real need for a device combining the favorable effects of DES on restenosis and a DAPT course of only 1 month when necessary.

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